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A STUDY OF THE CHANGES IN THE BLOOD COAGULATION
SYSTEM IN BURN DISEASE

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A STUDY OF THE CHANGES IN THE BLOOD COAGULATION
SYSTEM IN BURN DISEASE

Following is the translation of an article by V. N. Smidovich and L. I. Gerasimova entitled "Izucheniye Izmeneniy Svertyvayushchey Sistemy Krovi pri Ozhogovoy Bolezni" (English version above) in Khirurgiya (Surgery), Vol. 36, No. 5, 1960, pages 96-104.

From the Central Order of Lenin Institute of Hematology and Blood Transfusion (Director -- Member of the Academy of Medical Sciences USSR Prof. A. A. Bagdasarov) of the Ministry of Health USSR.

A number of authors have noted changes in the blood coagulating system in the presence of burns.

A. A. Spiridonov, with coauthors, has indicated a raised coagulation of the blood in the first 14 hours after a burn; S. A. Georgiyeva has also observed a shortening of the blood coagulation time in the first days after trauma. Blonska, Kamienski investigated the duration of the coagulation of heparinized blood in the course of burn disease. They detected that in the presence of severe and widespread burns an acceleration of the blood coagulation already ensues almost immediately after the influence of thermal trauma.

Many authors have noted a lowering of the content of plasma prothrombin in the presence of burns (V. I. Semenova, S. A. Georgiyeva, Anderson, Wolff and others). B. N. Postnikov indicates, that the lowering of the prothrombin in patients is the greater, the more widespread the area of the burn. On the other hand, James and others have observed great fluctuations in the prothrombin content of the plasma, but have not succeeded in noting any patterns in these changes.

In seven patients S. A. Georgiyeva determined the content of calcium of the plasma in the presence of burn disease and did not detect any deviations from normal.

Davidson and Matthew noted a considerable rise in the plasma fibrinogen after a burn, and the rise occurred not at once, but gradually with subsequent slow lowering as the patient recovered.

The thrombosis of the capillaries of the internal organs which arises in the first days of the disease. (V. Avdakov, O. K. Khmel'nitskiy) is a clinical manifestation of the disturbances of the blood coagulation in the presence of burn disease.

It follows from the literature data which have been presented that in the presence of burn disease only individual disturbances in the coagulation system of the blood have been noted. But, up to the present time no more detailed investigation of the changes of the blood coagulation system has been conducted, and, what is particularly important, the changes which have been observed were not associated with the conduct of the treatment. The study of these data was the object of the present work.

The following indexes were determined in patients: the time of coagulation of the blood according to the Fonio method (normal 20-30 minutes), if venopuncture proved to be impossible (collapse of the veins, burn of the extremities), the time of coagulation was determined by the Moas and Magro method (normal 6-12 minutes); fibrinogen -- by the dry-air method, worked out in our institute by R. A. Rotberg (The conversion into milligram-percentages is achieved by multiplying the weight quantity of fibrinogen in milligrams obtained from one ml by the coefficient 22.2); prothrombin -- by the Quick method (a single stage method, the thromboplastin is obtained from the gray matter of the human brain); the time of recalcification and the thrombin time -- by the Sirman method; the tolerance to heparin -- by the Sigg method; in addition, the retraction of the blood clot and the hematocrit volume were determined. The blood for investigation was taken from the vein upon admission of the patient, in the course of the further examination the blood was taken in the morning on an empty stomach.

The blood coagulation system was studied in 38 patients with burn disease, who were in the surgical clinic of the Institute (Director - Professor D. M. Grozdov). The patients were distributed in groups corresponding to the area of the burn: the first group (seven patients) with a burn area up to 10% of the total body surface; the second group (11 patients) with burns of from 11 to 20% of the body surface and the third group (20 patients) with burns of from 21 to 82% of the body surface.

The investigation of the changes of the blood coagulation system was basically conducted in the first 15-20 days after the burn, in a number of severely sick patients the examination was more prolonged (up to 195 days).

In all 38 patients investigated a complex treatment of the burn disease was conducted, the character of which ensued

from the evaluation of the general state of the patient, the level of the hemodynamic indexes, the area and the degree of the burn injury, the age of the patient and the given clinico-laboratory indexes.

The treatment of seven patients of the first group with burns of the first-second degree reduced to the primary surgical treatment of the burn wounds with the application of heterogeneous fibrin films or of a 6% emulsion of sulfidine; of the general therapeutic agents the patients received polyvitamins, cardiac and anesthetic preparations. On the 12th day of the disease the first bandaging was performed, at which time the complete epithelization of the burn wounds was detected.

Of the 11 patients of the second group, three patients had burns of the first-second degree, seven patients had burns of the second-third degree, and one patient burns of the second-third-fourth degree. Intravenous infusions of blood substitutes in doses of from 0.5 to one liter was performed for disintoxication purposes in five patients in whom the disease proceeded in a lighter form. In the other six patients of this group, phenomena of burn shock were observed and greater doses of blood substitutes were infused intravenously for them (from 1.5 to 3 liters per day for the course of the first three days of the disease).

Of the 20 patients of the third group with maximally severe burns, eight patients had injuries of 21-30% of the body surface, four patients - 31-40%, five patients - 41-50%, and three patients - 75-82%. Two patients had burns of the first-second degree, 10 patients had burns of the second-third degree, and eight patients of the second-third-fourth degree. Seventeen patients were admitted in a state of burn shock, from which 15 patients were successfully brought out, and two died (one patient in the first day and one on the third day from the moment of trauma).

The phase of intoxication was sharply expressed in all patients, and, in spite of the active therapy with the use of massive doses of antishock and disintoxication preparations in this phase, two patients died (on the fifth and sixth day), 50% of the surface of whose bodies had been burned. A septic phase was observed in 16 patients.

An active antishock and disintoxication therapy was conducted for the patients with the use of large doses of blood and blood substitutes of complex and directed action: polyglucin, neocompensan, blood and serum of convalescents, protein hydrolysates and the heteroprotein preparation BK-8.

In the course of the first three days of the disease the patients, as a rule, received up to three liters of liquid.

Subsequently we conducted the therapy depending on the clinical state.

Results of the investigation. In four patients of the first group, a shortening of the blood coagulation time was observed in the first days of the disease (maximally up to eight minutes by the Fonio method). At later periods of the disease, there were no deviations from the normal; the examination of the patients of this group was conducted up to 12 days after the burn. The blood coagulation time remained within normal limits in three patients.

In the second group, which included 11 patients, a rise in the blood coagulation in the first days after the burn was detected in nine patients (up to 8-10 minutes by the Fonio method). Subsequently the blood coagulation was normal, sometimes somewhat accelerated in five patients. In six severely sick patients, who had received large doses of blood substitutes, the blood coagulation was changed depending on the treatment which was used. In five of them in the course of 15-35 days after trauma the blood coagulation time fluctuated within limits below the normal boundary, but on individual days it was considerably shortened, which in individual patients coincided with cessation of the administration of the blood substitutes, in others proceeded against a background of continuing infusions and was not associated with change in the clinical state of the patient (transplantation of the skin, complications of the burn disease). Such patients received heparin. Let us present an example to illustrate what has been said.

Patient Ye. (burn of 11% of the body surface, of the second-third degree) in the course of the first 33 days of the disease received 10 liters of TsOLIPK /Central Order of Lenin Institute of Hematology and Blood Transfusion/ hydrolysate, 3 liters of 5% glucose solution. On a background of normal blood coagulation time a shortening was observed on the second day (13 minutes by the Fonio method), the 17th day (four and one half minutes by the Mack and Magro method), the 21st day (two and a half minutes by the Moas and Magro method) and on the 33rd day of the disease (12 and a half minutes by the Fonio method). The shortening of the blood coagulation time on the second day after trauma appears to be usual, but the shortening on the 17th, 21st and 33rd day set in on a background of daily infusion in doses of 0.5 liters of TsOLIPK hydrolysate, and no change in the state of the patient was noted in these days.

In the sixth patient a lengthening of the blood coagulation time was observed in the period during which BK-8 was infused.

The third group included patients who were maximally

sick. A rise in the blood coagulation in the first days after the burn was observed in all the patients of this group, with the exception of those, from whom blood for analysis was taken after the beginning of intravenous infusions; the limiting shortening of the blood coagulation was five minutes by the Fonio method. In subsequent days the picture of the changes of the blood coagulation was varied. In a majority of the patients the blood coagulation was acutely shortened only on individual days as a result of the active therapy.

In five patients, for whom infusions of large doses of BK-8 were conducted, a retardation of the blood coagulation was observed in the period during which this blood substitute was infused.

Data are presented in the table concerning patient Ye. (burn of 30 percent of the body surface of the second-third degree). From the second to the sixth day of the disease BK-8 was infused into the patient. In this period the coagulation time was sharply lengthened. It is important to note, that on the sixth day hemorrhage arose from the burn surface. In the septic period (from the 11th to the 22nd day), a shortening of the coagulation time was observed in the given patient.

The blood coagulation time was also shortened in the septic period in a number of other patients, sometimes reaching very low figures. In the periods of such a sharp rise in the blood coagulation, the patients were treated by the administration of heparin.

The data, obtained in the study of the plasma prothrombin level, are presented in Fig. 1. The quantity of prothrombin in the patients of the first group was found within limits close to normal, with the exception of one sharp lowering and one rise in the first days after the burn. It is of interest to note, however, that in the first days the prothrombin level was higher, than in the subsequent days. In patients of the second group the prothrombin was also found in normal limits in the overwhelming majority of the cases. However, both an increase in the first days of the disease, and also a lowering in the subsequent days was noted more often among these patients, than among the patients of the first group. In the majority of cases the prothrombin level was not lowered below 80 percent. The maximal lowering of the prothrombin ordinarily coincided with a slowing of the blood coagulation as a result of transfusion of BK-8, and then the quantity of prothrombin was again increased. In the third group disturbances in the content of prothrombin were more acutely expressed both in the direction of diminution, and also of increase. But it is necessary to note that even in

Day of disease	Coagulation time by the Fonio method	Prothrombin index (in %)	Fibrinogen (in mg %)	Recalcification time (in seconds)	Tolerance to heparin (in minutes and seconds)
1	8 minutes 30 seconds	100	311	120	5 minutes 35 seconds
3	One hour 30 minutes	47.2	466	375	20 minutes 30 seconds
4	One hour 15 minutes	53	868	280	10 minutes 30 seconds
5	One hour 03 minutes	47	932	200	20 minutes
6	2 hours 26 minutes	-	-	-	-
11	9 minutes	91	910	225	7 minutes
13	10 minutes	106	777	155	6 minutes
17	19 minutes	91	555	185	6 minutes
21	14 minutes	107	622	95	7 minutes
22	10 minutes	113	622	135	6 minutes
24	5 minutes 30 seconds by the Moas and Magro method	-	-	-	-

Table continued on next page

Retraction		Hematocrit	Day of Treatment after the burn	Therapy
in ml of the squeezed-out serum 0.39	in % of the plasma volume			
0.39	84	44/56	1*	One liter of polyglucin, one liter of physiological solution with glucose
Coagulation did not ensue		52/48	2	One liter of BK-8, 0.5 liters of physiological solution with glucose
The same		50/50	3	2 liters of BK-8, 300 ml of native plasma, 50 ml of convalescent plasma
The same		44/56	4	One liter BK-8, one liter of 5% glucose
The same		-	5	One liter BK-8, 120 ml of convalescent plasma
0.52	72	28/72	6	1,750 ml BK-8
-	-	28/72	7	0.5 liter of dry plasma
0.55	92	30/70	8	225 ml of convalescent plasma
0.57	80	29/71	9	1,250 ml of TsOLIPK /Central Order of Lenin Institute of Hematology and Blood Transfusion/hydrolysate
0.49	75	35/65	11	0.5 liters of dry plasma
-	-	-	12	250 ml of dry serum
-	-	-	13	250 ml of dry serum
			17	225 ml of erythrocyte mass
			21	225 ml of blood
			22	225 ml of blood

* The first investigation was conducted before the beginning of the infusions

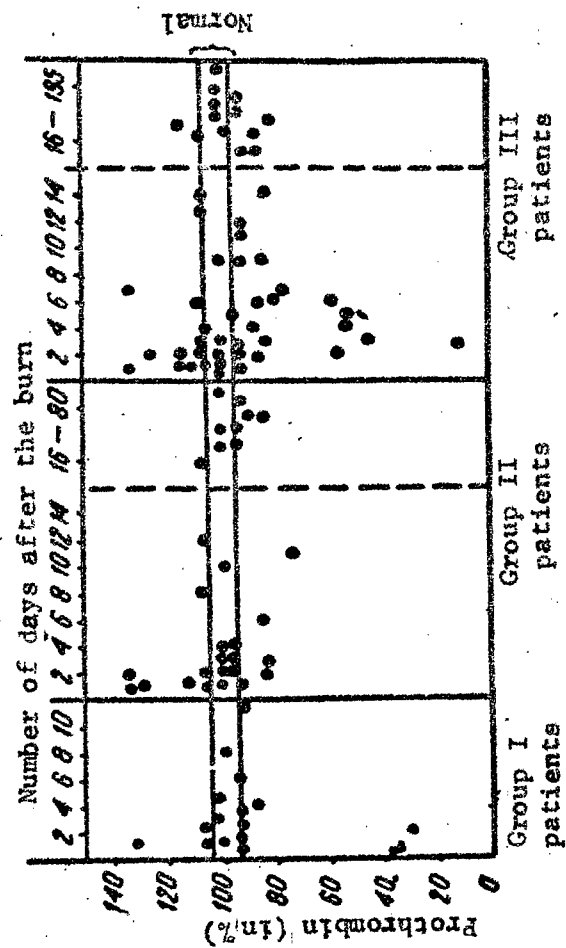


FIG. 1.

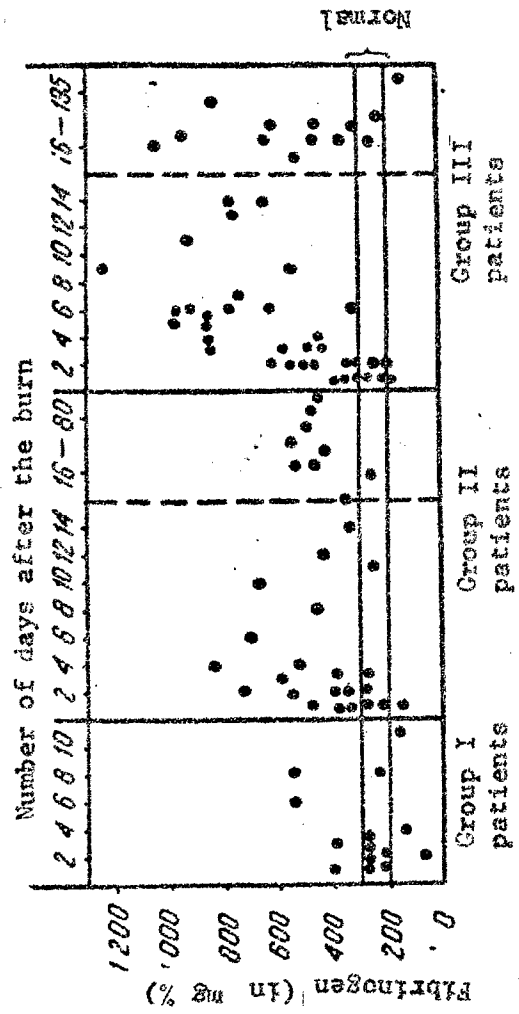


Fig. 2.

this group of severely sick patients, a lowering of the prothrombin level below 70 percent was observed only in the period of transfusion of BK-8 and of acute slowing of the blood coagulation (see Table).

The changes in the quantity of the plasma fibrinogen in the patients are presented on Fig. 2. The quantity of fibrinogen was insignificantly increased in patients of the first group, was more significantly increased both quantitatively and also in time in patients of the second group, and a maximal increase was noted in patients of the third group. The increase in the fibrinogen proceeded gradually, reaching maximal values on the fourth to the ninth day of the disease with a slow subsequent lowering. The degree of increase was directly proportional to the severity of the burn. The therapy which was used did not influence the dynamics of the change in the quantity of fibrinogen.

The recalcification time (normally 90-250 seconds) and the thrombin time (normally 28-40 seconds) fluctuated in normal limits with rare exceptions. A parallelism was noted in the change of these indexes and of the blood coagulation: when the blood coagulation time was shortened, there occurred a shortening of the recalcification time and the prothrombin time -- they fluctuated within the limits of the lower boundary of the normal range; when the blood coagulation was retarded after infusions of BK-8, both indexes were increased, sometimes exceeding the upper boundary of the normal range.

The tolerance for heparin (normally 7-12 minutes) was variously changed after the burn: the capacity of the blood coagulating system to counteract heparin introduced from without was either acutely diminished, or was increased both in the first days, and also in the period of toxemia and septicemia. We did not succeed in noting definite patterns in the changes of this index depending on the severity of the trauma and the treatment being conducted, other than a sharp increase in the tolerance for heparin in the period of the use of BK-8.

An analysis of the data obtained in the determination of the retraction of the blood clot has shown that in absolute figures the quantity of serum squeezed out fluctuates sharply, but if one refers the quantity of serum squeezed out to the quantity of plasma obtained in the hematocrit, then this ratio barely emerges from normal limits (see the table; normally, according to our data, this ratio fluctuates rather widely -- from 75 to 85%). A pronounced clotting of the blood (according to the indexes of the hematocrit and the quantity of erythrocytes) was observed in all patients in the first days after the burn. Subsequently, with the onset

of dilution of the blood, anemia developed in the patients, which sometimes was continued for a long time. The rise in the blood coagulation in the first days did not always coincide with the clotting period, and in later periods of the disease the blood coagulation was changed independently of the hemoconcentration.

The changes in the blood coagulation which are observed in the presence of burn disease, as it seems to us, can not arise under the influence of one factor alone. According to current views, the process of coagulation of the blood is extraordinarily complex and depends on many causes. The dependence of the blood coagulation on endocrine and humoral influences and on the functional state of the organism (N. V. Bogoyavlenskaya) has been solidly established. The participation in this process of the cerebral cortex has also been established (A. A. Markosyan).

B. A. Kudryashov attaches great significance to the state of the anticoagulating systems found outside the blood stream. Pain (N. S. Dzhevadyan), excitation of the sympathico-adrenal system (D. M. Zubairov), arising immediately after the burn evoke a rise in the blood coagulation. In addition, in the presence of burns the functions of various organs and systems of the organism, including the central nervous system, are disturbed, which is undoubtedly reflected in the blood coagulation process both in the sense of direct influence, and also in relation to the elaboration of various elements of the coagulation system. It is further well-known, that pain, strong emotional excitation (Ye. S. Vorob'yeva), excitation of the sympathetic nervous system (Ye. S. Ivanitskiy-Vasilenko) and other shifts observed in the presence of burns evoke an increase in the quantity of prothrombin. In addition, N. A. Belov notes that after a burn the quantity of prothrombin is increased in the first four to six days. The entire complex of these phenomena also occasions a rise in the blood coagulation after a burn. We have observed after the primary acute shortening, a lengthening of the blood coagulation time often up to the normal limits; it is possible that this proceeded under the influence of the therapy which was being used. When large doses of BK-8 are infused, the blood coagulation is sharply retarded. This property of the given blood substitute has also been noted by other authors (M. L. Garfunkel' and L. A. Danilova, N. A. Messineva and co-authors). It appears to be particularly negative in the presence of burn disease, since after a burn the permeability of the vessels is disturbed (K. F. Dogayeva and S. I. Itkin), and there are indications in the literature, that the permeability of the vessels is raised when the coagulability of

the blood is lowered (Witte). Thus, the transfusion of BK-8 can increase the loss of plasma from the vascular stream. It follows from this, that the transfusion of BK-8, particularly in large doses, in the presence of burn disease can have a negative influence on the state of the coagulating system of the blood. The rise in the coagulation of the blood which was sometimes observed in the septic period, as it seems to us, can be occasioned by the prolonged use of certain therapeutic agents which influence the state of the coagulating system. For example, penicillin, and also intravenous administrations of ascorbic acid can raise the coagulability of the blood (S. I. Zolotukhin; S. G. Aptekar' and K. M. Loriye).

The rise in the plasma prothrombin level which was noted by us in the first days after the burn was occasioned by those same factors as also the rise in the coagulation of the blood. In the presence of toxemia the quantity of prothrombin was diminished in the septic period. In patients with light forms of burn disease this lowering was insignificantly expressed and often did not emerge from normal limits; in severely sick patients the quantity of prothrombin rarely was below 70 percent, cases of greater lowering ordinarily coincided with a slowing in the blood coagulation evoked by transfusion of BK-8. Data are presented in the literature concerning a stable and significant lowering of the prothrombin of up to 38 percent in the presence of burn disease (B. N. Postnikov). We assume that this discrepancy can be explained by the effectiveness of the therapy which was used and which prevented disturbance of the liver function.

Inasmuch as the prothrombin formation appears to be a function of the liver, it suffered less in our patients. This assumption of ours coincides with the opinion of Bull and England who noted that certain changes which had previously been considered as typical in the presence of burns (severe azotemia, hyperkalemia, anuria, and acute tubular necroses), have become rare at the present time.

The prothrombin level did not always correspond to a rise in the coagulation of the blood; in these cases there evidently occurred a change in the factors which participate in the blood coagulation process, but which are not included in the prothrombin complex.

The increase in the fibrinogen which was observed was more pronounced in the presence of burns with a broad area of injury. It was not connected in time either with an acceleration of the blood coagulation, or with an increase in the prothrombin. An increase in fibrinogen, which is formed in the cells of the reticuloendothelial system, is usually observed in the presence of diseases which are accom-

panied by break-down of cells; in the presence of acute inflammatory and suppurative processes (A. A. Kovalevskiy). Burns evoke a generalized breakdown of protein (D. Ye. Ryvkina); in addition, the absorption of the products of protein breakdown proceeds for a long time from the burn surface. On the basis of what has been said above, the increase in fibrinogen in the presence of burns appears natural.

Inasmuch as the changes of the other indexes which have been studied by us are less substantial, we shall not dwell on them.

Conclusions

1. The following changes occurred in the coagulating system of the blood in patients with burn disease.

a) In the first to the second days of the disease the coagulation time was shortened under the influence of the burn trauma in almost all patients in direct dependence on the severity of the burn. In the period of toxemia, under the influence of the treatment which is being conducted, the coagulation time was normalized and in a majority of the patients fluctuated within limits of the lower boundary of the normal range; in a number of patients a considerable lengthening of the coagulation time (up to two hours) was noted during the infusion of large doses of BK-8. In the septic period in individual patients the coagulation time was shortened which was evidently occasioned by the prolonged use of certain medicinal substances (penicillin, ascorbic acid).

b) The plasma prothrombin level was increased in the presence of burn disease in the first days of the disease with subsequent lowering. In patients with light forms of burn disease these fluctuations were insignificant; in severely sick patients the range of the fluctuations was increased.

c) The quantity of fibrinogen of the plasma gradually increased, reaching maximal magnitudes on the fourth to the ninth day of the disease; the increase was directly proportional to the severity of the burn and sometimes reached 1,000 mg%. A gradual lowering of the fibrinogen was subsequently observed. The treatment which was used did not influence the dynamics of the changes in the fibrinogen.

2. Taking into account that there are disturbances in the coagulating system of the blood in the presence of burn disease, we consider it expedient to conduct a determination of the blood coagulation time in the course of the entire

disease with the object of the opportune use of appropriate therapy (transfusion of blood substitutes, the administration of heparin).

3. The transfusion of blood substitutes (polyglucin, neokompensan, protein hydrolyzates), with the exception of BK-8, exerts a positive action on the state of the coagulating system in patients with burn disease (normalization of the coagulation time). In addition, their use improves the liver function, which is positively reflected in the prothrombin formation.

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